REMARKS

Upon entry of the foregoing amendments claims 24, 27, 28, and 38-46 are pending. No new matter has been added. Claims 24, 27 and 28 have been amended. Support for the amendments to claims 24, 27, and 28 may be found in claims 1-28 as originally filed as well as in Example 8, Example 9B and Table 3. Claims 38-46 are new claims. Support for new claims 38-46 is found in claims 1-28 as originally filed, in the specification at ¶¶ [0099] through [0105]; FIG. 2 and FIG. 22. Support for the types of malignancies treated is found throughout the specification, as well as in Examples 12, and 15, 16, 17 and 18.

Claims 26, 29, and 35-37 have been cancelled without prejudice. The Applicants reserve the rights to file continuation or divisional applications directed to the subject matter for all withdrawn/canceled claims. Consideration and allowance of the pending claims is hereby requested in view of the above amendments and the following remarks.

Priority, Information Disclosure Statement and Drawings

The Applicants thank the Examiner for acknowledging the foreign priority claim, information disclosure statement and accepting the drawings submitted on 12/15/2004.

Claim Objections

The Examiner objected to claim 24 for reciting "administering isolated". The Applicants submit that this objection is moot as amended claim 24 no longer recites "administering isolated".

The Examiner objected to claim 24 for reciting "wherein said arginase comprising chemical modification". The Applicants submit that this objection is moot as amended claim 24 no longer recites "wherein said arginase comprising chemical modification".

The Examiner objected to claim 24 for reciting "half-life for". The Applicants submit that this objection is moot as amended claim 24 no longer recites "half-life for".

The Examiner objected to claim 28 for reciting "treatment malignancies". The Applicants submit that this objection is moot as amended claim 24 no longer recites "treatment malignancies".

The Examiner objected to claim 29 for reciting "of protein". The Applicants submit that this objection

is obviated by the cancellation of claim 29 by present amendment.

The Examiner objected to claim 32 for reciting "comprising isolated". The Applicants submit that this objection is obviated by the cancellation of claim 32 by present amendment.

The Examiner objected to claim 36 for reciting "of protein". The Applicants submit that this objection is obviated by the cancellation of claim 36 by present amendment.

For the foregoing reasons, the Applicants respectfully request the Examiner reconsider and withdraw the objections to the above referenced claims.

Claim Rejections

35 U.S.C. §112, Second Paragraph

The Examiner rejected claim 29 and claim 36 under 35 U.S.C. §112, second paragraph. The Examiner reasons that recitation of "method is performed in absence of protein breakdown inhibitor renders the claim unclear with regard to it's metes and bounds. The Applicants submit that this rejection is obviated by the cancellation of claims 29 and 36 by present amendment. In light of these amendments the Applicants respectfully request reconsideration and withdrawal of the rejection of claim 29 and claim 36 under 35 U.S.C. §112, second paragraph.

35 U.S.C. §112, First Paragraph

Written Description

The Examiner rejected claims 24, 26-29, 32 and 35-37 under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. The Examiner reasons that the claims contain subject matter, which was not described in the specification in such a way as to reasonable convey to one skilled in the relevant art that the Applicants, at the time the application was filed, had possession of the claimed invention. The Applicants submit that this rejection is obviated, in part, by the cancellation of claims 26, 29, 32 and 35-37 by present amendment. The Applicants note that claims 24, 27 and 28 are pending.

The Examiner rejected claims 24, 27 and 28 for lacking structural description that would result in the recited characteristics of, for example, extended half-life. Claim 24 as amended is drawn to "a method of

treatment of human liver, breast, colon or rectal malignancies, comprising administering to a subject a modified, full-length recombinant human arginase I polypeptide of 80-100% purity which is covalently linked to at least one polyethylene glycol (PEG) molecule." Claims 27 depends from claim 24 and recites the limitation that the modified, full-length recombinant human arginase I polypeptide has an extended half-life of at least 3 days duration. Claim 28 as amended is directed to "a method of treatment of human liver, breast, colon or rectal malignancies, comprising administering to a subject in need thereof a modified, full-length recombinant human arginase l polypeptide, which is covalently linked to at least one polyethylene glycol (PEG) molecule, wherein the administration of the modified, full-length recombinant human arginase l polypeptide reduces the physiological arginine level in the subject to below 10 μM for at least 3 days." In accordance with the Examiner's helpful suggestion (see Office Action at page 6, ¶3), these claims have been limited to the polypeptide modification disclosed in the specification, *i.e.*, pegylated, full-length, recombinant human arginase I, as detailed in Examples 8 through 12 of the specification as filed. The Applicants submit that claims 24, 27 and 28 as amended define a genus of pegylated polypeptides such that one skilled in the relevant art would recognize that the Applicants, had possession of the claimed invention at the time the application was filed. As such, the Applicants submit that, amended claims 24, 27 and 28 which are in full compliance with the written description requirement of 35 U.S.C. §112, first paragraph. The Applicants respectfully request reconsideration and withdrawal of rejection of claims 24, 27 and 28 for lack of written description under 35 U.S.C. §112, first paragraph.

Enablement

The Examiner rejected claims 24, 26-29, 32 and 35-37 under 35 U.S.C. §112, first paragraph, as failing to comply with the enablement requirement. The Examiner reasons that the specification does not enable any person of skill in the art to which it pertains, or which it is most nearly connected, to make and use the invention commensurate with the above-referenced claims. (Office Action at p. 8, ¶1). The Examiner acknowledges that the specification is enabling for a method of treatment of human malignancies comprising administering a pegylated form of a polypeptide comprising a full-length, recombinant human arginase I

(*e.g.*, SEQ ID NO. 9). (Office Action at p. 8, ¶1).

The Applicants submit that this rejection is obviated, in part, by the cancellation of claims 26, 29, 32 and 35-37 by present amendment. The Applicants note that claims 24, 27 and 28 are pending. As noted above, claim 24 as amended is drawn to "a method of treatment of human liver, breast, colon or rectal malignancies, comprising administering to a subject a modified, full-length recombinant human arginase I polypeptide of 80-100% purity which is covalently linked to at least one polyethylene glycol (PEG) molecule." Claims 27 depends from claim 24 and recites the limitation that the modified, full-length recombinant human arginase I polypeptide has an extended half-life of at least 3 days duration. Claim 28 as amended is directed to "a method of treatment of human liver, breast, colon or rectal malignancies, comprising administering to a subject in need thereof a modified, full-length recombinant human arginase I polypeptide, which is covalently linked to at least one polyethylene glycol (PEG) molecule, wherein the administration of the modified, full-length recombinant human arginase I polypeptide reduces the physiological arginine level in the subject to below 10 μM for at least 3 days."

The Applicants submit that amended claims 24, 27 and 28 are commensurate in scope with subject matter acknowledged as enabled by the specification as filed. That is, a method of treatment of specified human malignancies comprising administering a pegylated form of a polypeptide comprising a full-length, recombinant human arginase I (*e.g.*, SEQ ID NO. 9). (see Office Action at p. 8, ¶1). As such, the Applicants submit that amended claim 24, claim 27 and claim 28, are in full compliance with the enablement requirement of 35 U.S.C. §112, first paragraph. The Applicants respectfully request reconsideration and withdrawal of the rejection of claims 24, 27 and 28 for lack of enablement under 35 U.S.C. §112, first paragraph.

35 U.S.C. §102(e)—Anticipation in view of Tepic *et al.* (WO/2003/063780)

The Examiner has rejected claims 28, 29 and 37 under 35 U.S.C. §102(e) as being anticipated by Tepic *et al.* (WO/2003/063780) claiming priority of provisional application 60/350,971 filed on 1/25/2002. The Applicants submit that this rejection is obviated, in part, by the cancellation of claims 29 and 37 by present

amendment. Claim 28 as amended is directed to "a method of treatment of human liver, breast, colon or rectal malignancies, comprising administering to a subject in need thereof a modified, full-length recombinant human arginase I polypeptide, which is covalently linked to at least one polyethylene glycol (PEG) molecule, wherein the administration of the modified, full-length recombinant human arginase I polypeptide reduces the physiological arginine level in the subject to below 10 μM for at least 3 days." The Applicants traverse the rejection of claim 28 as anticipated by Tepic *et al.* pursuant to MPEP §706.02 and MPEP §2136 by antedating the priority date of Tepic *et al.* (*i.e.*, January 25, 2002). The Applicants submit evidence of the prior invention of the method of claim 28 prior to January 25, 2002 in a declaration pursuant to 37 C.F.R. Rule 1.131 filed herewith[1]. As stated in the Declaration, the Applicants were in possession of modified, full-length recombinant human arginase I polypeptide covalently linked to at least one polyethylene glycol (PEG) molecule prior to January 25, 2002. (See Rule 1.131 Declaration at p. 2, ¶ 5). Furthermore, modified, full-length recombinant human arginase I polypeptide compositions covalently linked to at least one polyethylene glycol (PEG) molecule were administered by the Applicants to treat a human subject with malignancy (rectal carcinoma) prior to January 25, 2002. (See Rule 1.131 Declaration at p. 2, ¶¶ 4-6; Exhibits A through D; as well as Examples 9A and 12, ¶¶ [0099]-[0102]; ¶¶ [0128]-[0136]; FIGS. 21 and 28 of the specification as filed; see US 2005/0244398). It is noteworthy that Example 12 of the specification as filed recites the use of a pegylated arginase I composition as early as August 2001 in a method of treating malignancy in a female subject. (see Example 12, ¶¶ [0129]-[0136]; FIGS. 21, 28 and 29 of the specification as filed; see US 2005/0244398). As such, the Applicants submit that Tepic *et al.* is disqualified as prior art to the claimed invention as the Applicants have provided evidence to establish a reduction to practice of the claimed invention prior to the critical date for Tepic *et al.* Accordingly, the Applicants respectfully request that the rejection of amended claim 28 pursuant to 35 U.S.C. §102(e) be

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[1] All the dates have been redacted from Exhibit A through Exhibit D pursuant to MPEP §715.07. The name of the subject has been partially redacted in the Exhibits to protect the subject's identity.

withdrawn.

35 U.S.C. §103—Obviousness: Tepic *et al.* in view of Ikemoto *et al.*

The Examiner rejected claims 24, 26-27, 32 and 35-36 under 35 U.S.C. §103(a) as being unpatentable over Tepic *et al.*(WO/2003/063780) in view of Ikemoto *et al.*, Biochem. J., 270(3): 697-703 (1990). The Examiner reasons that in light of the combination of the teaching of these references, the subject matter of the claims is rendered obvious to one of ordinary skill in the art at the time of the invention was made to derive a more purified arginase protein to be used in the method of treating cancer taught by Tepic *et al.* (Office Action at p. 14, ¶2). The Applicants submit that this rejection is obviated, in part, by the cancellation of claims 26, 29, 32 and 35-36 by present amendment. The Applicants note that claims 24 and 27 are pending. Claim 24 as amended is drawn to "a method of treatment of human liver, breast, colon or rectal malignancies, comprising administering to a subject a modified, full-length recombinant human arginase I polypeptide of 80-100% purity which is covalently linked to at least one polyethylene glycol (PEG) molecule." Claim 27 which depends from claim 24, recites the limitations that the extended half-life is of at least 3 days duration.

The Applicants submit that the rejection of amended claims 24 and 27 pursuant to 35 U.S.C. §103(a) as being unpatentable over Tepic *et al.*(WO/2003/063780) in view of Ikemoto *et al.*, Biochem. J., 270(3): 697-703 (1990) is improper. The Applicants traverse the rejection of claim 24 and 27 as anticipated by Tepic *et al.* pursuant to MPEP §706.02 and MPEP §2136 by antedating the priority date of Tepic *et al.* (*i.e.*, January 25, 2002). The Applicants submit evidence of prior invention of the method of claim 28 prior to January 25, 2002 in a declaration pursuant to 37 C.F.R. Rule 1.131. As stated above, (see section "35 U.S.C. §102(e)—Anticipation in view of Tepic et al. (WO/2003/063780)") and as detailed in the Rule 1.131 Declaration and Exhibits A-D filed herewith, the Applicants document that they were in possession of a method of treating human malignancy by administering to a subject a modified, full-length recombinant human arginase I polypeptide which is covalently linked to at least one polyethylene glycol (PEG) molecule prior to the critical reference date of Tepic *et al.* afforded pursuant to 35 U.S.C. §102(e) (claiming benefit of

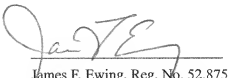
priority to provisional application 60/350,971 filed on 1/25/2002). The Applicants further declare that the subject matter which is described and now claimed in the above-identified application was pursued by the Applicants with due diligence from the acts described in the Exhibits which are prior to the critical reference date of Tepic *et al.* through to filing of the above-identified application, *e.g.*, the subject matter of amended claims 24 and 27. (see also, Examples 9, 12, and 15-18; as well as; FIGs. 21 through 29 of the specification as filed; see US 2005/0244398). Accordingly, the Applicants submit that Tepic *et al.* is disqualified as prior art to the claimed invention. Further, the teachings of Ikemoto *et al.* do not cure the deficiencies of Tepic *et al.* Accordingly, the Applicants respectfully request that the rejection of amended claims 24 and 27 pursuant to 35 U.S.C. §103(a) as being unpatentable over Tepic *et al.* in view of Ikemoto *et al.* be withdrawn as the Applicants antedate Tepic *et al.*

CONCLUSION

In view of the above amendments and remarks this application is believed to be in condition for allowance. If there are any questions regarding these amendments and remarks, the Examiner is encouraged to contact the undersigned at the telephone number provided below.

Respectfully submitted,

Dated: January 27, 2008



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